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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,043	03/01/2006	Martin Fussenegger	2006-0153A	6327

513 7590 01/29/2010

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EXAMINER
LEAVITT, MARIA GOMEZ

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
01/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,043	FUSSENEGGER ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,9-27 and 29* is/are pending in the application.

4a) Of the above claim(s) *10-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,9 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 09-30-2009 has been entered.
3. Status of claims. Claims 2-4, 9-27 and 29 are pending. Claim 1 has been cancelled, claims 2-4 and 9 have been amended and claim 29 has been added by Applicant's amendment filed on 09-30-2009. Claims 10-27 were previously withdrawn from consideration as being directed to non-elected invention pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim. Because applicant did not distinctly and specifically pointed out the supposed errors in the restriction requirement, the election was previously treated as an election **without traverse** (MPEP § 818.03(a)).
4. Therefore, claims 2-4, 9 and 29 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn Rejections in response to Applicants' arguments or amendments

Claim objection

In view of Applicants' cancellation of claim 1, objection to claim 1 is rendered moot. In view of Applicants' amendment of claim 2, objection to claim 2 has been withdrawn.

Claim Rejections - 35 USC § 112-second paragraph

In view of Applicants' cancellation of claim 1, rejection of claim 1 and dependent claims 2-4 and 9 under 35 U.S.C. 112, second paragraph, is rendered moot.

Claim Rejections - 35 USC § 103

In view of Applicants' amendment of the claims to recite in independent claim 29, a nucleic acid encoding an acetaldehyde-responsive *Aspergillus nidulans* AlcR protein, rejection of claims 2, 4 and 9 under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999, of record) has been withdrawn.

Though the combined disclosure of Caddick and White teaches or suggest an isolated mammalian cell comprising a nucleic acid encoding an ethanol-responsive *Aspergillus nidulans* AlcR protein, it fails to teach or suggest an acetaldehyde-responsive *Aspergillus nidulans* AlcR protein (e.g., *Aspergillus nidulans* AlcR protein that binds to the corresponding alcA gene promoter in response to acetaldehyde).

Rejections/objections maintained in response to Applicants' arguments or amendments

35 USC § 112- First paragraph- Scope of enablement

Claims 2-4 and 9 remain rejected and claim 29 is newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

An isolated mammalian cell comprising,

(a) a nucleic acid comprising a promoter said promoter operatively linked a nucleic acid sequence encoding an acetaldehyde- responsive transcription factor AlcR protein, and

(b) a nucleic acid comprising a promoter said promoter operatively linked to an *A. nidulans* AlcR-specific P_{AlcA} operator sequence obtained by amplifying said operator site P_{AlcA} sequence from a P_{AlcA} containing vector with oligonucleotides of SEQ ID No. 1 and SEQ ID No. 2,

does not reasonably provide enablement for a mammalian host cell comprising the transcription factor AlcR protein wherein said *Aspergillus nidulans* AlcR protein is expressed without being functionally linked to a promoter for transcriptional expression.

Response to Applicants' arguments as they relate to rejection of claims 2-4, 9 and 29 under 35 USC § 103

At page 8 of the remarks filed on 09-30-2009, Applicants essentially argue that new claim 29 has been amended to recite to what is considered enabled by the examiner. Such is not persuasive.

New claim 29, subpart (a) does not place any limitation on a nucleic acid encoding an acetaldehyde-response *Aspergillus nidulans* AlcR protein being functionally linked to a regulatory sequence. To the extent that the specification describes solely one example of an expression vector encoding the *Aspergillus nidulans* AlcR protein under the control of a promoter mediating constitutive expression of the AlcR protein in CHO cells, and furthermore, to the extent that the art is unpredictable with regard to expression of a gene that is not functionally linked to a promoter, it would have required undue experimentation to practice the instant invention to identify an enormous number of mammalian cells as broadly or generically claimed, with a resultant identification of mammalian cells comprising an *Aspergillus nidulans* AlcR protein expressed from the encoding nucleic acid sequence without being operationally linked to a promoter to specifically bind and transcriptionally activate the corresponding *A. nidulans* P_{AlcA} operator sites located in a promoter in a separate nucleic acid molecule.

Claim Rejections - 35 USC § 103

Claim 3 remains rejected and claims 2, 4, 9 and 29 are newly rejected under 35 USC 103 as being unpatentable over Caddick et al., US Patent No. 6,605,754, (Date of Issue August 12, 2003) in view of White (Internet article November 11, 1999) and further in view of Flipphi et al., (*Bichem. J.* 2002, pp. 25-31).

In addition to the disclosure of the combined references of Caddick, White and Flipphi set forth at pages 9-13 of the office action filed on 06-30-2009, Caddick et al., teaches that *Aspergillus nidulans* expresses the enzyme alcohol dehydrogenase I (ADH1) encoded by the gene *alcA* only when it is grown in the presence of various alcohols and ketones (col. 2, lines 65-67). The induction is relayed through a regulator protein encoded by the alcR gene and constitutively expressed. In the presence of inducer (alcohol or ketone), the regulator protein activates the expression of the alcA gene. Thus the *alcA* gene promoter (the *alcA* gene encodes alcohol dehydrogenase I) is an inducible promoter which is activated by the alcR regulator protein (e.g., responsive transcription factor) in the presence of inducer or a regulating compound such as protein/alcohol or protein/ketone combination (col. 2, lines 65-67 bridging to col. 3, lines 1-4) Additionally, Flipphi discloses as inducers of the *alc* genes: primary alcohols e.g., ethanol, primary monoamines, the amino acid L-threonine and ketones. All ethanol, ethylamine and L-threonine routes of degradation converge on acetaldehyde as the common catabolic intermediate.

Therefore in view of the benefits of using the ethanol-inducible *alcR* gene expression system (e.g., time point of induction, expression level, duration of expression) in a variety of plants, as taught by Caddick et al., it would have been *prima facie* obvious for one of ordinary skill in the art to use mammalian host cells to study the ethanol-induce *alcR* gene expression

system, particularly because White MRH suggests transfecting mammalian cells with expression vectors expressing the *A. nidulans*-derived AlcR transcription factor, and *A. nidulans alcA* promoter which is induced in the presence of ethanol. The AlcR protein activates expression from *alcA* gene by binding to specific sites in *alcA*. Moreover, it would have been *prima facie* obvious for one of ordinary skill in the art to use the alcA/alcR gene activation system wherein *Aspergillus nidulans* AlcR protein binds to the corresponding response elements in the alcA gene in the presence of various known inducers of the *alc* genes as taught by Flipphi including acetaldehyde.

Response to Applicants' arguments as they relate to rejection of claims 2, 4, 9 and 29 under 35 USC § 103

At pages 8-10 of the remarks filed on 09-30-2009, Applicants essentially argue that: 1) the disclosure of White is defective because isolated mammalian cells are not expected to metabolize ethanol to aldehyde, 2) Caddick merely discloses a chemically-inducible plant gene expression cassette comprising a first promoter, e.g., the *alcA* gene promoter (the *alcA* gene encodes alcohol dehydrogenase I) operably linked to a regulator sequence which encodes a regulator protein, e.g., AlcR regulator protein (the transcription factor), whereby said alcR gene product is induced by an effective exogenous inducer, i.e., by the protein/alcohol/ or protein/ketone combination whereas in the instant invention the formation of the AlcR protein is dissected from the alcohol dehydrogenase, 3) the proposed system of White is just a project that is not functional since ethanol is not a direct inducer of the AlcR system and would instead require metabolization into acetaldehyde to be induction effective which does not occur in standard mammal cells, 4) although in liver and brain cells ethanol is metabolized to

acetaldehyde, an isolated mammalian cell comprising exogenous nucleic acid is clearly different from primary brain and liver cells as evidenced by the disclosure of Clemens et al (Archives of Biochemistry and Biophysics 321, 311-318; 1995; Attachment A) which shows that cultured hepatocytes lose their ability to metabolize ethanol to acetaldehyde, and 5) Eysseric et al., (Alcoholism: Clinical and Experimental Research 21, 1018-1023, 1997) demonstrates production of acetaldehyde by astrocytic primary cells, no by astrocytes containing exogenous nucleic acid. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1) and 3), White explicitly teaches the use of mammalian host cells to be transfected with an expression vector encoding the *Aspergillus nidulans*-derived AlcR transcription factor which in the presence of ethanol (e.g., inducer or a regulating compound) activates transcription from promoters containing specific operator sites from *A. nidulans alcA* promoter. Flipphi complements the teachings of Caddick and White by disclosing that induction by ethanol, l-threonine and ethylamine can only be ascribed to acetaldehyde. Note that ethanol is oxidized to acetaldehyde via alcohol dehydrogenase. Both plants and mammalian cells express alcohol dehydrogenase (adh) encoded by the *alcA* gene which is responsible for the oxidation of ethanol to acetate via acetaldehyde. So if incubation with ethanol of transiently transformed maize protoplasts plants with the *alcA*-CAT reporter and the *alcR*-cDNA regulator cassette induces CAT gene expression, incubation with ethanol of transiently transformed mammalian cells with *Aspergillus nidulans alc*A-*alc*R system should be reasonably expected to regulated the ethanol-inducible *alcR* gene expression system for the same reason ethanol induces the *Aspergillus nidulans alc*A-*alc*R system in plants, both alcohol dehydrogenase in plant and mammalian cells effectively metabolize ethanol into acetaldehyde. In addition, the use of

prokaryotic transcriptional regulatory elements for controlled expression of cloned genes in mammalian cells and animals was well known in the art as evidenced by the use of the *Streptomyces*-derived butyrolactone-responsive quorum-sensing systems to adjust transgene expression in mammalian cells and mice (Weber, 2003; Nucleic Acids Res. 2003 July 15; 31(14): e71) further supporting the use of the ethanol –inducible transgene expression *Aspergillus nidulans* AlcA/AlcR system in the White publication.

Regarding 2) the fact that that Caddick discloses a chemically-inducible plant gene expression cassette comprising a first promoter operatively linked to a sequence comprising an alcR coding sequence from *Aspergillus nidulans* which encodes an AlcR regulator protein and an inducible promoter from the *alcA* gene from Aspergillus nidulans operatively linked to a target gene, the inducible promoter being activated by the AlcR regulator protein in the presence of an alcohol and/or ketone inducer is not disputed. However, the subject of a regulator protein (e.g., responsive transcription factor) and a target gene being in the same gene expression cassette rather than in two separate and independent constructs is not significantly relevant in view that Caddick teaches two different genes expressed from two different promoters, e.g., a first promoter linked to a gene comprising the alcR coding sequence and an inducible promoter operatively linked to a target gene, the inducible promoter from an *alcA* gene being activated by the AlcR regulator protein in the presence of an inducer. Thus, there is not reason why a nucleic acid encoding the AlcR regulator protein (claim 29, (a)) and a nucleic acid comprising a promoter said promoter operatively linked to an *A. nidulans* AlcR-specific P_{AlcA} operator sequence (claim 29, (b)) couldn't be expressed from separate nucleic acid molecules as easily as from a gene expression cassettes comprising both genes transcriptionally activated by a first

constitutively active first promoter and a second inducible promoter. Furthermore, note that claim 29 does not place any limitation on whether the nucleic acid encoding an acetaldehyde-responsive transcription factor AlcR protein is operationally linked to a promoter, let alone whether the AlcR protein is expressed.

Regarding 4) and 5), the instant claims do not place any limitations on whether any of the genes encoded by the nucleic acids recited in claim 29, steps (a) and (b) are expressed. All what claim 29 requires is an isolated mammalian cell comprising a nucleic acid encoding an acetaldehyde-responsive *A. nidulans* AlcR protein and a second nucleic acid *A. nidulans* AlcR-specific P_{AlcA} operator sequence. There is not requirement for the alcA/alcR gene activation system to be functional nor the inducer to be present. Thus Applicants' arguments in relation to ethanol being an indirect inducer of the AlcR system are irrelevant to the claimed invention. Moreover, the instant claims broadly embrace an isolated mammalian cell which does not preclude isolated primary cells lines. Additionally, the isolated mammalian cell is not required to be a recombinant hepatic cell line stably expressing alcohol dehydrogenase. All the necessary elements of the claimed invention related to an isolated cell transformed with expression vectors comprising alcA/alcR gene activation system and transformation of mammalian cell were known in the art at the time the invention was made. Flipphi provides the motivation to use acetaldehyde as an inducer so in its presence the AlcR protein activates the *alc* genes.

References made of record in a PTO-892 Form to complete the record

Marchitti et al., 2008, Expert Opinion on Drug Metabolism & Toxicology, pp. 697-720.
Pateman et al., *Proc R Soc Lond B Biol Sci.* 1983 pp.243-64

Conclusion

Claims 2-4, 9 and 29 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633